REMARKS

Claim 1 has been rewritten as new claim 21 to restrict the scope of the claim to inhibiting myeloperoxidase activity in neutrophils using enterolactone. Claim 6 has been amended to depend from new claim 21. Claims 2-5, 17 and 18 have been canceled. New claims 22 and 23 have been added to claim other aspects of the invention previously found in claim 1. Support for new claims 22 and 23 can be found in the claims as originally filed and throughout the specification. It is submitted that these amendments do not constitute new matter and their entry is requested.

Objection

The Examiner objected to the abstract of the disclosure because the abstract is not limited to a single paragraph. Applicants have amended the abstract to comply with the requirements of MPEP §608.01(b). Withdrawal of this rejection is requested.

Claim Rejections under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1 and 4 are rejected under 35 U.S.C. § 112, first paragraph, containing subject matter which the examiner is of the opinion was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. More specifically, the examiner argues that "the overactivity that is inhibited is lifespan controlled by Fas-mediated apoptosis" limitation in claim 1 is new matter.

In view of the rewriting of claim 1 as new claim 21 and the cancellation of claim 4, it is submitted that this rejection has been obviated. Withdrawal of this rejection is requested.

Claim Rejection under 35 U.S.C. § 102(a)

The Examiner rejected claim 1 under 35 U.S.C. §102(a) as being anticipated by Yesilada et al. (*Cytokine* 13(6):359-364, March 2001). The Examiner contends that Yesilada et al. teaches a

method of inhibiting the overactivity of phagocytes or lymphocytes such as peripheral blood of an individual which inherently contains lymphocytes and macrophages by administering these cells to a lignan such as matairesinol. According to the Examiner, Yesilada et al. also discloses the inhibition of TNF alpha production by the reference cells and matairesinol is useful for the treatment of rheumatoid arthritis by inhibiting TNF alpha production. Thus, the Examiner is of the opinion that Yesilada et al. anticipates the claimed invention.

Applicants submit a Declaration under Rule 1.131 herewith to remove the Yesilada reference as prior art. Applicants submit that some time on or prior to 21 March 2001 (the publication date of Yesilada et al.), the inhibition of overactivity of phagocytes by administering hydroxymatairesinol had been determined because human neutrophils were stimulated by addition of phorbol-myristate-acetate (PMS) to produce an oxidative burst. Furthermore, some time on or prior to 21 March 2001, the inhibition of overactivity of phagocytes by administering hydroxymatairesinol had been determined because a porcine neutrophil sample treated with hydroxymatairesinol was found to inhibit myeloperoxidase activity. Copies of laboratory notebook records evidencing the determination of the above inhibition activities are attached to the Declaration.

It is also submitted that new claim 21 obviates this rejection. Furthermore, with the submission of a Declaration under Rule 1.131, Applicants submit Yesilada et al. is removed as prior art, and is thus, not available as prior art under either the 35 U.S.C. §102(a) rejection and the 35 U.S.C. §103(a) rejection.

Claim Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 1-6, 17 and 18 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. 6,451,849 B1 ("'849 patent") in view of Morikawa et al. (*J Pharm Pharmacol* 44(10):859-61, 1992) or Yesilada et al. or Hirano et al. (*Life Science* 55(13):1061-69, 1994). The Examiner contends that the '849 patent teaches a method of administering to an individual an effective amount of lignan such as hydroxymatairesinol that has the same structure as

shown in claim 1. Morikawa et al., according to the Examiner, teaches enterolactone as inhibiting fMLP induced oxidative burst, such as superoxide production by human polymorphonuclear leukocytes. Finally, the examiner argues that Yesilada et al. reference teaches matairesinol as a lignan having a structure identical to the claimed matairesinol as an inhibitor of overactivity of phagocytes such as TNF alpha production by macrophages and peripheral blood lymphocytes. Thus, the Examiner reasons that it would have been obvious to one of ordinary skill in the art at the time the invention was made that the inhibition effect of hydroxymatairesinol and its metabolites such as enterolactone and matairesinol on lipid peroxidation as taught by the '849 patent is mediated by the cell type such as neutrophils as taught by Morikawa et al. and macrophages as taught by Yesilada et al. Finally, the Examiner states that one of ordinary skill in the art would have been motivated to do this because Yesilada et al. teaches that matairesinol is useful for inhibition of overactivity of phagocytes in rheumatoid arthritis, Morikawa et al. teaches enterolactone inhibits fMLP induced oxidative bursts, and the '849 patent teaches hydroxymatairesinol as useful for treating cancers.

Claim 1 has been rewritten as new claim 21, and claim 6 has been amended. Claims 2-5, 17 and 18 have been canceled, rendering the rejection as to these claims moot. Applicants submit that the submission of the Rule 1.131 Declaration removes Yesilada et al. as prior art under 35 U.S.C. §103(a).

The Examiner admits that the invention in claim 1 differs from the teachings of the references in that the method wherein the phagocytes are neutrophils, the lignan is enterolactone or the phagocytes are macrophages and the lignan is enterolactone or hydroxymatairesinol. Newly added claim 21 is directed to a method of inhibiting myeloperoxidase activity in neutrophils in an individual by administering an effective amount of enterolactone. Therefore, newly added claim 21 and dependent claim 6 obviate this rejection.

Even so, with regard to newly added claim 23, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The '849 patent and Morikawa et al. as combined, fail to teach that hydroxymatairesinol is able to decrease the formation *in vivo* of reactive

oxygen species, which in turn would cause lipid oxidation. This property, which is necessary for inhibition of oxidative burst or myeloperoxidase activity, is not suggested by the '849 patent. The '849 patent discloses that hydroxymatairesinol is a useful antioxidant because it is an inhibitor of lipid peroxidation and LDL oxidation. Furthermore, Morikawa et al. discloses that enterolactone inhibits fMLP induced oxidative burst in neutrophils. The references, as combined, fail to teach or suggest all the claim limitations of newly added claim 23.

There also must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine the references in the manner urged by the examiner. Nowhere in the references cited is there any motivation or a suggestion to inhibit oxidative burst or myeloperoxidase activity in neutrophils by administering hydroxymatairesinol. Nor is there an expectation of reasonable success. Rather, Morikawa et al. teaches that a concentration of 100 μM enterolactone reduced fMLP oxidative burst in neutrophils by 50%. The Examiner is of the opinion that the combination of Morikawa et al. for teaching cell types such as neutrophils and the effect of hydroxymatairesinol on lipid peroxidation as taught by the '849 patent would allow one to have a reasonable expectation of success in producing the claimed invention.

But Morikawa et al. also discloses other lignans, such as 2,3-dibenzylbutane-1,4-diol (DBB) as having a strong increasing effect on inhibition of fMLP induced oxidative burst in neutrophils, and a third lignan, prestegane B (Pre) as having no significant effect. Therefore, it is apparent that each lignan behaves individually. One could not reasonably expect to predict the effect of hydroxymatairesinol based on the teachings of Morikawa et al. in view of the disclosure of the '849 patent.

Accordingly, it is submitted that the claims of the present invention are not obvious in view of the references cited by the examiner. Withdrawal of this rejection is requested.

In view of the above amendments and remarks and in view of the Rule 131 Declaration, it is submitted that the claims are patentable over the prior art and comply with the patent statutes.

Reconsideration and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite allowance of this application.

Respectfully submitted,

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